US007745463B2

(12) **United States Patent**
Wang et al.

(10) **Patent No.: US 7,745,463 B2**
(45) **Date of Patent: *Jun. 29, 2010**

(54) **ALKENE PIPERIDINE DERIVATIVES AS ANTIVIRAL AGENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/484,407**

(22) Filed: **Jun. 15, 2009**

(65) **Prior Publication Data**

US 2009/0253741 A1 Oct. 8, 2009

Related U.S. Application Data

(62) Division of application No. 11/749,445, filed on May 16, 2007, now Pat. No. 7,572,810.

(60) Provisional application No. 60/811,898, filed on Jun. 8, 2006.

(51) **Int. Cl.**

A61K 31/445	(2006.01)
A61K 31/4545	(2006.01)
A61P 31/12	(2006.01)
C07D 215/20	(2006.01)
C07D 295/00	(2006.01)

(52) **U.S. Cl.** **514/314**; 514/330; 546/177

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

This disclosure provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the disclosure is concerned with alkene piperidine derivatives that possess unique antiviral activity. More particularly, the present disclosure relates to compounds useful for the treatment of HIV and AIDS.

4 Claims, No Drawings

ALKENE PIPERIDINE DERIVATIVES AS ANTIVIRAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This Divisional application claims the benefit of U.S. Ser. No. 11/749,445 filed May 16, 2007, now allowed, which in turn claims the benefit of U.S. Provisional Application Ser. No. 60/811,898 filed Jun. 8, 2006, now expired.

FIELD OF THE DISCLOSURE

This disclosure provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the disclosure is concerned with alkene piperidine derivatives that possess unique antiviral activity. More particularly, the present disclosure relates to compounds useful for the treatment of HIV and AIDS.

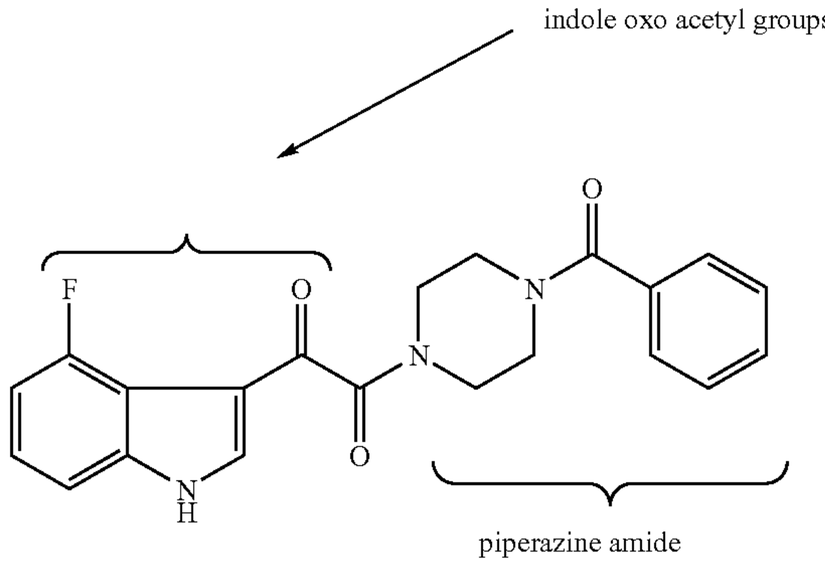
BACKGROUND ART

HIV-1 (human immunodeficiency virus-1) infection remains a major medical problem, with an estimated 40 million people infected worldwide at the end of 2005. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations: zidovudine (or AZT or Retrovir®), didanosine (or Videx®), stavudine (or Zerit®), lamivudine (or -3TC or Epivir®), zalcitabine (or DDC or Hivid®), abacavir succinate (or Ziagen®), Tenofovir disoproxil fumarate salt (or Viread®), emtricitabine (or FTC), Combivir® (contains -3TC plus AZT), Trizivir® (contains abacavir, lamivudine, and zidovudine), Epzicom® (contains abacavir and lamivudine), Truvada® (contains Viread® and emtricitabine); non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune®), delavirdine (or Rescriptor®) and efavirenz (or Sustiva®), and peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, and Kaletra®(lopinavir and Ritonavir). Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant

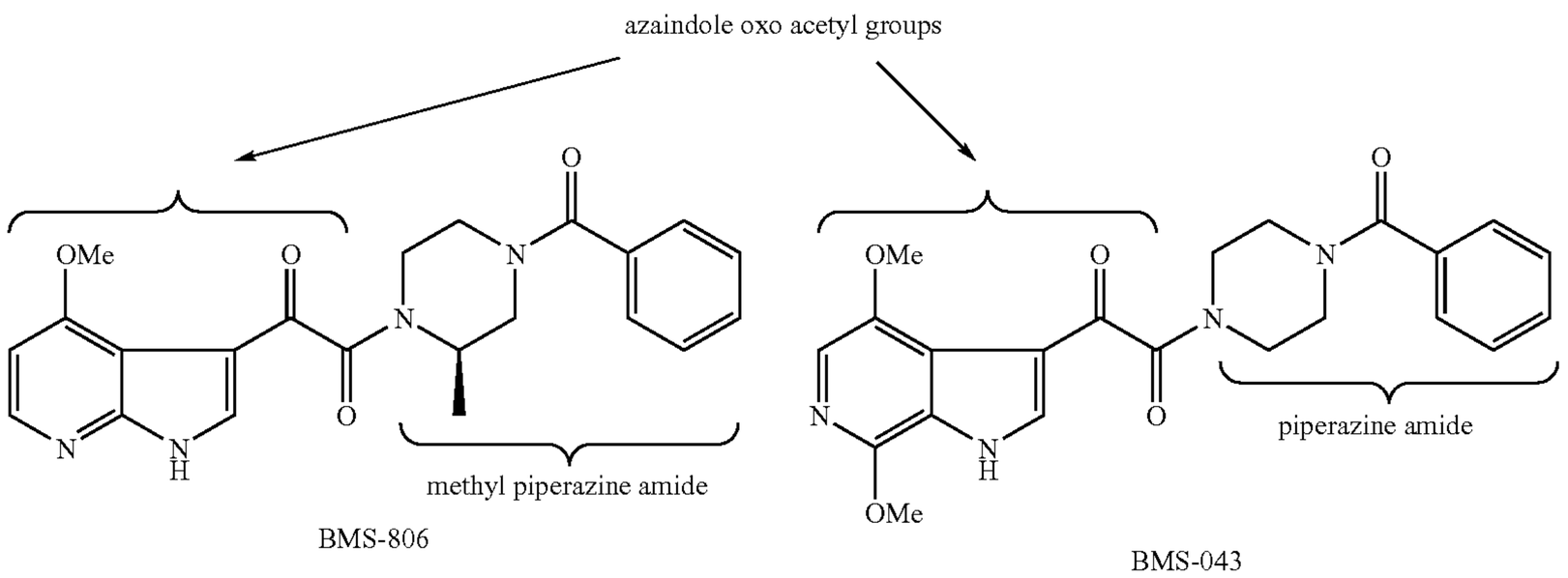
reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents currently being studied by a number of investigators.

The properties of a class of HIV entry inhibitors called HIV attachment inhibitors has been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents. A disclosure describing indoles of which the structure shown below for BMS-705 is representative has been disclosed [Antiviral Indoleoxoacetyl piperazine Derivatives].

BMS-705



Two other compounds, referred to in the literature as BMS-806 and BMS-043 have been described in both the academic and patent art:



Some description of their properties in human clinical trials have been disclosed in literature.

It should be noted that in all three of these structures, a piperazine amide (In these three structures a piperazine phenyl amide) is present and this group is directly attached to an oxoacetyl moiety. The oxoacetyl group is attached at the 3-position of 4-Fluoro indole in BMS-705 and to the 3 position of substituted azaindoles in BMS-806 and BMS-043.

In an effort to obtain improved anti-HIV compounds, later publications described in part, modified substitution patterns on the indoles and azaindoles. Examples of such effort include: (1) novel substituted indoleoxoacetic piperazine derivatives, (2) substituted piperazinyloxoacetylindole derivatives, and (3) substituted azaindoleoxoacetic piperazine derivatives.

Replacement of these groups with other heteroaromatics or substituted heteroaromatics or bicyclic hydrocarbons was also shown to be feasible. Examples include: (1) indole, azaindole and related heterocyclic amidopiperazine derivatives; (2) bicyclo 4.4.0 antiviral derivatives; and (3) diazaindole derivatives.

A select few replacements for the piperazine amide portion of the molecules have also been described in the art and among these examples are (1) some piperidine alkenes; (2) some pyrrolidine amides; (3) some N-aryl or heteroaryl piperazines; (4) some piperazinyl ureas; and (5) some carboline containing compounds.

Antiviral compounds containing piperidine alkenes are contained in the following published patent applications Wang, Tao; et. al. U.S. Pat. Appl. Publ. US 20040186292 A1 and Wang, et. al. U.S. Pat. Appl. Publ. US 20040063744 A1 but are structurally distinct from the compounds in this application.

Method(s) for preparing prodrugs for this class of compounds was disclosed in Prodrugs of piperazine and Substituted Piperidine Antiviral Agents (Ueda et al., U.S. nonprovisional application Ser. No. 11/066,745, filed Feb. 25, 2005 or US20050209246A1 or WO2005090367A1).

A published PCT patent application WO2003103607A1 (Jun. 11, 2003) disclosures an assay useful for assaying some HIV inhibitors.

Several published patent applications describe combination studies with piperazine benzamide inhibitors, for example, US20050215543 (WO2005102328A1), US20050215544 (WO2005102391A1), and US20050215545 (WO2005102392A2).

A publication on new compounds in this class of attachment inhibitors (Jinsong Wang et. al. Org. Biol. Chem. 2005, 3, 1781-1786.) and a patent application on some more remotely related compounds have appeared WO2005/016344 published on Feb. 24, 2005.

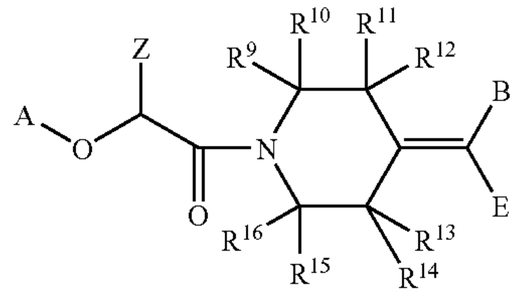
Published patent applications WO2005/016344 and WO2005/121094 also describe piperazine derivatives which are HIV inhibitors. The compounds described in these applications are structurally distinct from the compounds of the present disclosure.

Nothing in these references can be construed to disclose or suggest the novel compounds of this disclosure and their use to inhibit HIV infection.

SUMMARY OF THE DISCLOSURE

The present disclosure relates to compounds of Formula I, the pharmaceutically acceptable salts and/or solvates (e.g., hydrates) thereof, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I, their pharmaceutically acceptable salts and/or solvate are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

A first embodiment of the disclosure are compounds of Formula I, including pharmaceutically acceptable salts thereof,



I

wherein:

A is quinoline, isoquinoline, quinazolinyl, phenyl, indazolyl, benzoxazolyl, or pyridyl wherein said, isoquinoline, quinazolinyl, phenyl, indazolyl, benzoxazolyl, or pyridyl is substituted with from 1 to 3 substituents selected from C_{1-6} alkoxy, —$COOC_{1-3}$alkyl, C_{1-6}alkyl, $COONH_2$, CON$(COOC_{1-3}alkyl)_2$, $COONHC_{1-3}$alkyl, —$NHCH_2CH_2OH$, N$(C_{1-3}alkyl)_2$, NH$(C_{1-3}$alkyl), halogen, or pyrazolyl;

R^9-R^{16} are independently hydrogen or methyl with the proviso that no more than three are methyl and none are geminal (on the same carbon);

B is CN, $C(O)NH_2$, F, Cl, phenyl, oxazolyl, isozazolyl, pyrazolyl or oxadiazolyl wherein said phenyl, oxazolyl, isozazolyl, pyrazolyl or oxadiazolyl is optionally substituted with 1 to 2 halogen, amino, dimethyl amino, methylamino, or C_{1-3}alkyl;

E is phenyl, pyridyl, or pyrimidinyl;

Z is methyl where the configuration at the carbon where it is attached is either (S), (R), or a mixture of the two configurations.

Another embodiment of the present disclosure is a method for treating mammals infected with a virus, especially wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, and one or more pharmaceutically acceptable carriers, excipients or diluents; optionally the compound of Formula I can be administered in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

Another embodiment of the present disclosure is a pharmaceutical composition comprising an antiviral effective amount of a compound of Formula I and one or more pharmaceutically acceptable carriers, excipients, diluents and optionally in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

DETAILED DESCRIPTION OF THE DISCLOSURE

Since the compounds of the present disclosure, may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present disclosure includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I in addition to the mixtures thereof.

Definitions

The term "C_{1-6}alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

"Halogen" refers to chlorine, bromine, iodine or fluorine.

An "aryl" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and —NR^xR^y, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl, diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and —NR^xR^y, wherein R^x and R^y are as defined above.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encomplish systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and —NR^xR^y, wherein R^x and R^y are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, cycloheptane, cycloheptatriene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo-methanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and —NR^xR^y with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an —OH group.

An "alkoxy" group refers to both an —O-alkyl and an —O-cycloalkyl group as defined herein.

An "aryloxy" group refers to both an —O-aryl and an —O-heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl-O-group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic-O-group with heteroalicyclic as defined herein.

A "thiohydroxy" group refers to an —SH group.

A "thioalkoxy" group refers to both an S-alkyl and an —S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an —S-aryl and an —S-heteroaryl group, as defined herein.

A "thioheteroaryloxy" group refers to a heteroaryl-S-group with heteroaryl as defined herein.

A "thioheteroalicycloxy" group refers to a heteroalicyclic —S-group with heteroalicyclic as defined herein.

A "carbonyl" group refers to a —C(═O)—R" group, where R" is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An "aldehyde" group refers to a carbonyl group where R" is hydrogen.

A "thiocarbonyl" group refers to a —C(═S)—R" group, with R" as defined herein.

A "Keto" group refers to a —CC(═O)C-group wherein the carbon on either or both sides of the C═O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroaliacyclic group.

A "trihalomethanecarbonyl" group refers to a $Z_3CC(=O)$-group with said Z being a halogen.

A "C-carboxy" group refers to a —C(═O)O—R" groups, with R" as defined herein.

An "O-carboxy" group refers to a R"C(—O)O-group, with R" as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R" is hydrogen.

A "trihalomethyl" group refers to a $—CZ_3$, group wherein Z is a halogen group as defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$-groups with Z as defined above.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$-group with Z as defined above and R^x being H or (C_{1-6})alkyl.

A "sulfinyl" group refers to a —S(═O)—R" group, with R" being (C_{1-6})alkyl.

A "sulfonyl" group refers to a $—S(=O)_2R"$ group with R" being (C_{1-6})alkyl.

A "S-sulfonamido" group refers to a $—S(=O)_2NR^XR^Y$, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-Sulfonamido" group refers to a $R"S(=O)_2NR_X$-group, with R_x being H or (C_{1-6})alkyl.

A "O-carbamyl" group refers to a $—OC(=O)NR^xR^y$ group, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "O-thiocarbamyl" group refers to a $—OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$-group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "amino" group refers to an $—NH_2$ group.

A "C-amido" group refers to a $—C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "C-thioamido" group refers to a $—C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-amido" group refers to a $R^xC(=O)NR^y$-group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "ureido" group refers to a $—NR^xC(=O)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6}) alkyl.

A "guanidino" group refers to a $—R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6}) alkyl.

A "guanyl" group refers to a $R^xR^yNC(=N)$-group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "cyano" group refers to a —CN group.

A "silyl" group refers to a $—Si(R")_3$, with R" being (C_{1-6}) alkyl or phenyl.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6})alkyl.

A "hydrazino" group refers to a $—NR^xNR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

Physiologically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this disclosure. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris (hydroxymethyl)-aminomethane), or with bases such as piperidine or morpholine.

In the method of the present disclosure, the term "antiviral effective amount" means the total amount of each active component of the method that is sufficient to show a meaningful patient benefit, i.e., healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing or ameliorating diseases associated with HIV infection.

The present disclosure is also directed to combinations of the compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following table.

Drug Name	Manufacturer	Indication
	ANTIVIRALS	
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)

-continued

Drug Name	Manufacturer	Indication
Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	Sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266, Sustiva ®) (−)6-Chloro-4-(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex

-continued

Drug Name	Manufacturer	Indication
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread ®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)

-continued

Drug Name	Manufacturer	Indication
Emtriva ® (Emtricitabine)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
Combivir ®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Abacavir succinate (or Ziagen ®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Reyataz ® (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDs, protease inhibitor
Fuzeon ® (or T-20)	Roche/Trimeris	HIV infection AIDs, viral Fusion inhibitor
Lexiva ® (or Fosamprenavir calcium)	GSK/Vertex	HIV infection AIDs, viral protease inhibitor
Maraviroc; (UK 427857)	Pfizer	HIV infection AIDs, (CCR5 antagonist, in development)
Trizivir ®	GSK	HIV infection AIDs, (three drug combination)
PA-457	Panacos	HIV infection AIDs, (maturation Inhibitor, in development)
Sch-417690 (vicriviroc)	Schering-Plough	HIV infection AIDs, (CCR5 antagonist, in development)
TAK-652	Takeda	HIV infection AIDs, (CCR5 antagonist, in development)
GSK 873140 ONO-4128)	GSK/ONO	HIV infection AIDs, (CCR5 antagonist, in development)
BMS-707035	Bristol-Myers Squibb	HIV infection AIDs, (viral integrase Inhibitor)
Integrase Inhibitor MK-0518	Merck	HIV infection AIDs, viral integrase inhibitor in development
Truvada ®	Gilead	Combination of Tenofovir disoproxil fumarate salt (Viread ®) and Emtriva ® (Emtricitabine)
Integrase Inhibitor GS917/JTK-303	Gilead/Japan Tobacco	HIV Infection AIDs, viral integrase inhibitor in development
Triple drug combination	Gilead/Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (Viread ®), Emtriva ® (Emtricitabine), and Sustiva ® (Efavirenz)
IMMUNOMODULATORS		
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS

-continued

Drug Name	Manufacturer	Indication
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon
ANTI-INFECTIVES		
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulene	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis

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Drug Name	Manufacturer	Indication
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the disclosure herein may be used in combination with another class of agents for treating AIDS which are called HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194 and *Inhibitors of the entry of HIV into host cells*. Meanwell, Nicholas A.; Kadow, John F. Current Opinion in Drug Discovery & Development (2003), 6 (4), 451-461. Specifically the compounds can be utilized in combination with other attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor.

It will be understood that the scope of combinations of the compounds of this disclosure with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table but includes, in principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is Reyataz® (active ingredient Atazanavir). Typically a dose of 300 to 600 mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500 mgs). Another preferred inhibitor of HIV protease is Kaletra®. Another useful inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-1-(4-(3-pyridyl-methyl)-2(S)—N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. Pat. No. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present disclosure and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

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In such combinations the compound of the present disclosure and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

Abbreviations

The following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, are

used throughout the description of the disclosure and the examples. Some of the abbreviations used are as follows:

h =	hour(s)
rt =	room temperature
mol =	mole(s)
mmol =	millimole(s)
g =	gram(s)
mg =	milligram(s)
mL =	milliliter(s)
TFA =	trifluoroacetic Acid
DCE =	1,2-Dichloroethane
CH_2Cl_2 =	dichloromethane
TPAP =	tetrapropylammonium perruthenate
THF =	tetrahydofuran
DEPBT =	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DMAP =	4-dimethylaminopyridine
P-EDC =	polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDC =	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
DMF =	N,N-dimethylformamide
Hunig's Base =	N,N-diisopropylethylamine
MCPBA =	meta-chloroperbenzoic Acid
azaindole =	1H-pyrrolo-pyridine
4-azaindole =	1H-pyrrolo[3,2-b]pyridine
5-azaindole =	1H-pyrrolo[3,2-c]pyridine
6-azaindole =	1H-pyrrolo[2,3-c]pyridine
7-azaindole =	1H-pyrrolo[2,3-b]pyridine
PMB =	4-methoxybenzyl
DDQ =	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
OTf =	trifluoromethanesulfonoxy
NMM =	4-methylmorpholine
PIP-COPh =	1-benzoylpiperazine
NaHMDS =	sodium hexamethyldisilazide
EDAC =	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
TMS =	trimethylsilyl
DCM =	dichloromethane
DCE =	dichloroethane
MeOH =	methanol
THF =	tetrahydrofuran
EtOAc =	ethyl acetate
LDA =	lithium diisopropylamide
TMP-Li =	2,2,6,6-tetramethylpiperidinyl lithium
DME =	dimethoxyethane
DIBALH =	diisobutylaluminum hydride
HOBT =	1-hydroxybenzotriazole
CBZ =	benzyloxycarbonyl
PCC =	pyridinium chlorochromate

The compounds of the present disclosure may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and diluents.

Thus, in accordance with the present disclosure, there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of the present disclosure.

The pharmaceutical composition may be in the form of orally administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this disclosure can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

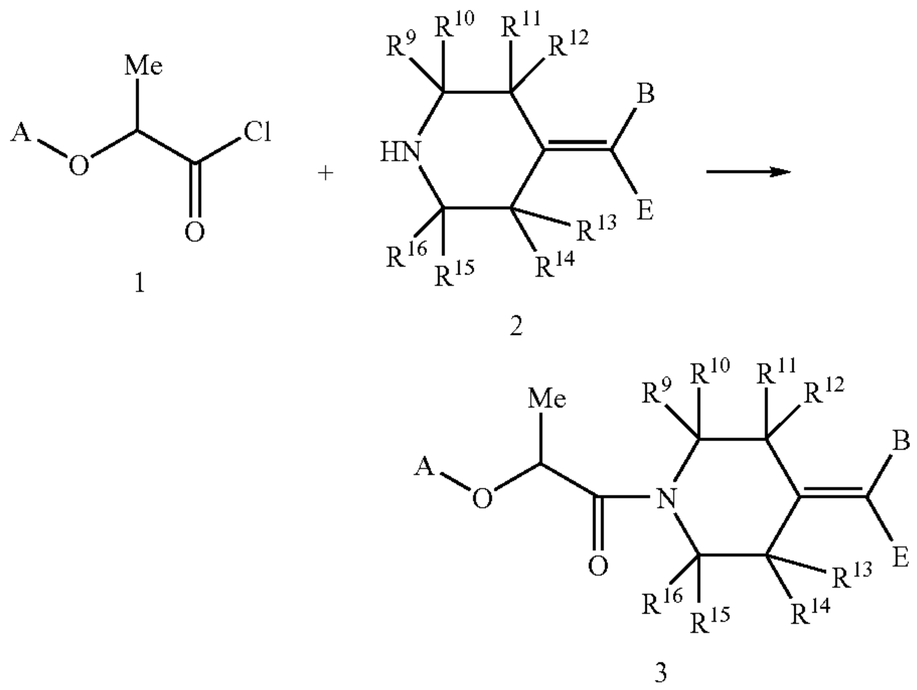
CHEMISTRY

The present disclosure comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof. General procedures to construct compounds of Formula I and intermediates useful for their synthesis are described in the following Schemes.

Preparation of Compounds of Formula I

A chemist skilled in the art is aware of many standard conditions for reacting an amine with an acyl halide 1 (Scheme 1) and carboxyl acid 4 (Scheme 2) that could be used to convert the acid chloride or acid to the desired amide products. Some general references of these methodologies and directions for use are contained in "Comprehensive Organic Transformation" by Richard C. Larock, Wiley-VCH, New York, 1989, 972 (Carboxylic acids to amides), 979 (Acid halides to amides).

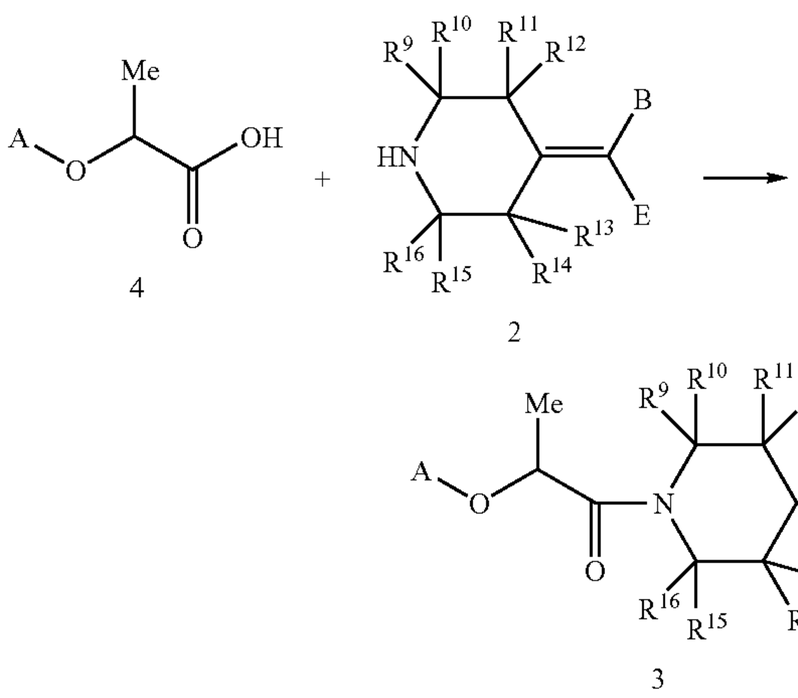
Scheme 1



Scheme 1 depicts a general method for forming an amide from piperidine alkene 2 and acyl chloride 1. An appropriate base (from catalytic to an excess amount) selected from sodium hydride, potassium carbonate, triethylamine, DBU, pyridine, DMAP or di-isopropyl ethyl amine was added into a solution of agent 2 and acyl chloride in an appropriate

solvent selected from dichloromethane, chloroform, benzene, toluene, THF, diethyl ether, dioxane, acetone, N,N-dimethylformamide or pyridine at room temperature. The reaction was carried out at either room temperature or experimentally determined optimum temperature up to 150° C. over a period of time (30 minutes to 16 hours) to afford compounds 3 which may either be compounds of formula I or precursors. Some selected references involving such reactions include a) Indian J. Chem., Sect B 1990, 29, 1077; 2) Chem. Sci. 1998, 53, 1216; 3) Chem. Pharm. Bull. 1992, 40, 1481; 4) Chem. Heterocycl. Compd. 2002, 38, 539.

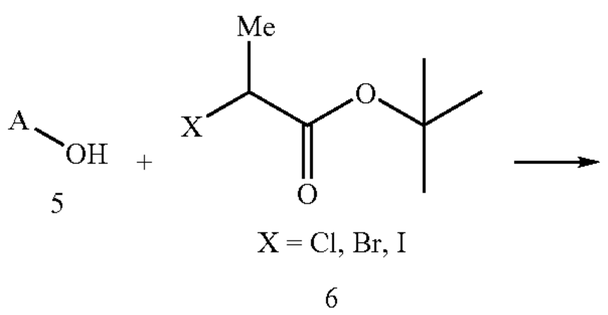
Scheme 2



Alternatively, as shown in Scheme 2, structure 2 can be coupled with an acid 4 using standard amide bond or peptide bond forming coupling reagents. Many reagents for amide bond couplings are known by an organic chemist skilled in the art and nearly all of these are applicable for realizing coupled amide products. The combination of EDAC and triethylamine in tetrahydrofuran or BOPCl and diisopropyl ethyl amine in chloroform have been utilized most frequently but DEPBT, or other coupling reagents such as PyBop could be utilized. Another useful coupling condition employs HATU ((a) J. Chem. Soc. Chem. Comm. 1994, 201; (b) J. Am. Chem. Soc. 1994, 116, 11580). Additionally, DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one) and N,N-diisopropylethylamine, commonly known as Hunig's base, represents another efficient method to form the amide bond and provide compounds of Formula I. DEPBT is either purchased from Adrich or prepared according to the procedure described in Organic Lett., 1999, 1, 91. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used.

The general agent 2 used in Schemes 1 and 2, are either commercially available or may be prepared according to procedures described in detail in US-2004/0063744.

Scheme 3



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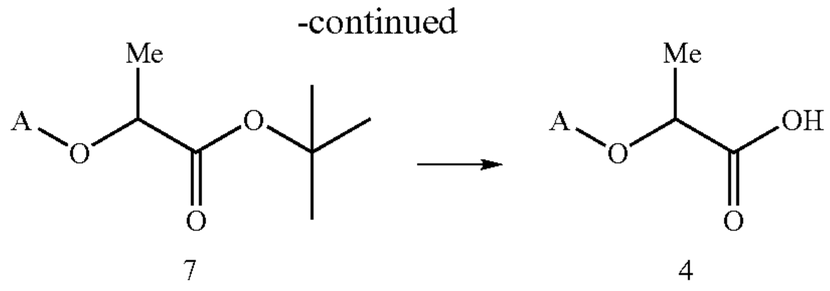
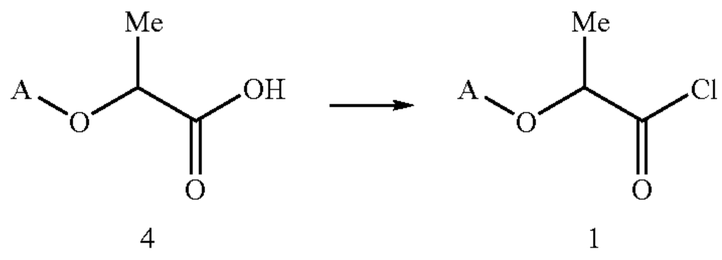


Scheme 3 describes a general route towards the structure of intermediate 4. Alcohol 5 couples with a t-butyl 2-halo propanoic ester with a base selected from NaH, KH, LiHMDS, NaHMDS, KHMDS, Li_2CO_3, Na_2CO_3, K_2CO_3, Ce_2CO_3 in an aprotic solvent. Typically an inert solvent such as DMF, THF, DME, dioxane, DMSO is used but other aprotic solvents could be used. The Boc group is removed under acidic solution would provide a 2-keto piperazine amide intermediate. TFA and HCl are the typical solvents, while the most commonly used solvents are ether and dichloromethane, but other acidic agents and solvents could be used.

Scheme 4



As shown in Scheme 4, intermediate 1 can be prepared from intermediate 4 by using $SOCl_2$, ClCOCOCl or $POCl_3$ with or without solvent. When a solvent is used, typical solvent is CH_2Cl_2 or $ClCH_2CH_2Cl$, but other aprotic solvents could be used.

EXAMPLES

The following examples illustrate typical syntheses of the compounds of Formula I as described generally above. These examples are illustrative only and are not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Chemistry

Typical Procedures and Characterization of Selected Examples:

Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ^1H NMR spectra were recorded on Bruker DRX-500 f at 500 MHz (or Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The chemical shifts were reported in ppm on the δ scale relative to δTMS=0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), and DMSO-d6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (J) is in Hertz.

All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

Analytical LC-MS Method:

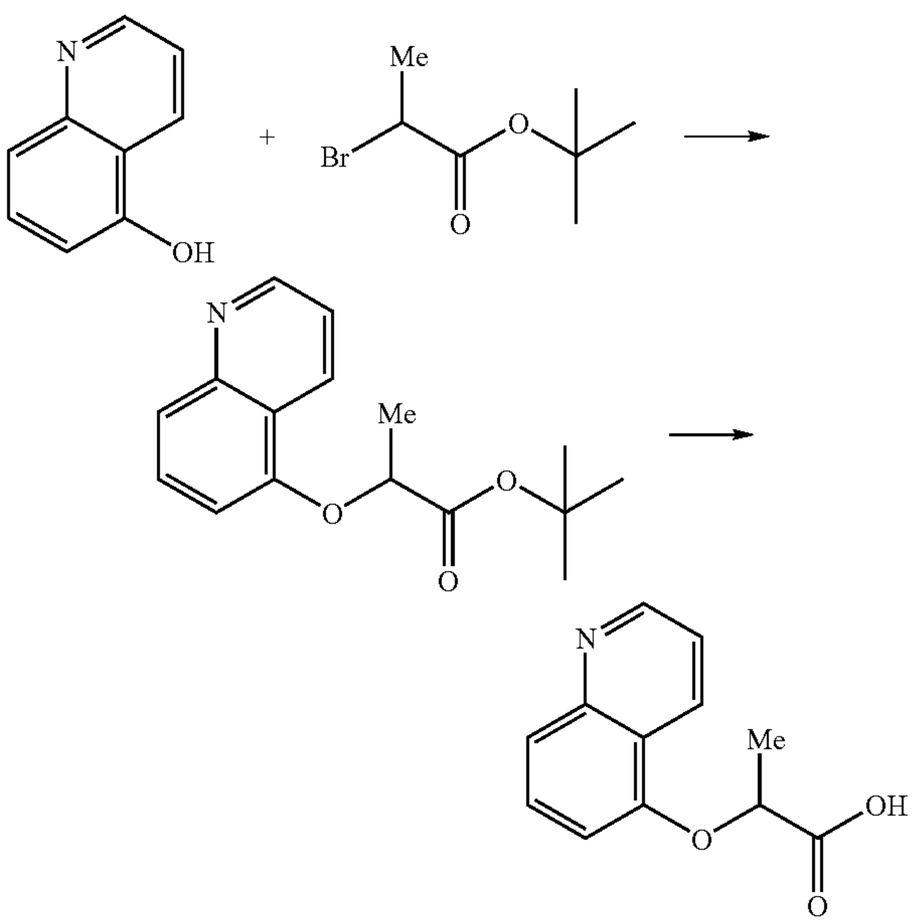
Method A:
Column A: Xterra 2.1×50 mm 5 um C18
Solvent: A=Water, B=ACN, Modifier=10 mM NH_4OAc
Gradient: 0.00'=10% B, 0.80'=60% B, 1.99'=95% B, 2.00' (1.5 mL/min)=100% B, 2.56'=100% B, 2.74'=10% B
Flow rate: 1 ml/min
Detector Wavelength: 220 nm

Method B:
Column B: Phenomenex-Luna 4.6×50 mm S10
Start % B=0
Final % B=100
Solvent: A=10% MeOH/90% H2O/0.1% TFA
Solvent: B=90% MeOH/10% H2O/0.1% TFA
Gradient time: 4 min
Flow rate: 4 ml/min
Detector Wavelength: 220 nm

HPLC Purification Method:
Compounds purified by preparative HPLC were diluted in DMF (1.5 ml) and purified using the following methods on a Waters automated preparative HPLC system.
Column C: Xbridge 19×50 mm 5 um C18
Solvent: A=Water, B=ACN, Modifier=10 mM NH_4OAc
Method: 25 mL/min, 0'=10% B, 0.5' (12.5 mL/min)=10% B, 2' (12.5 mL/min)=10% B, 2.5'=10% B, 9.3'=95% B, 12'=95% B
Detector Wavelength: 220 nm

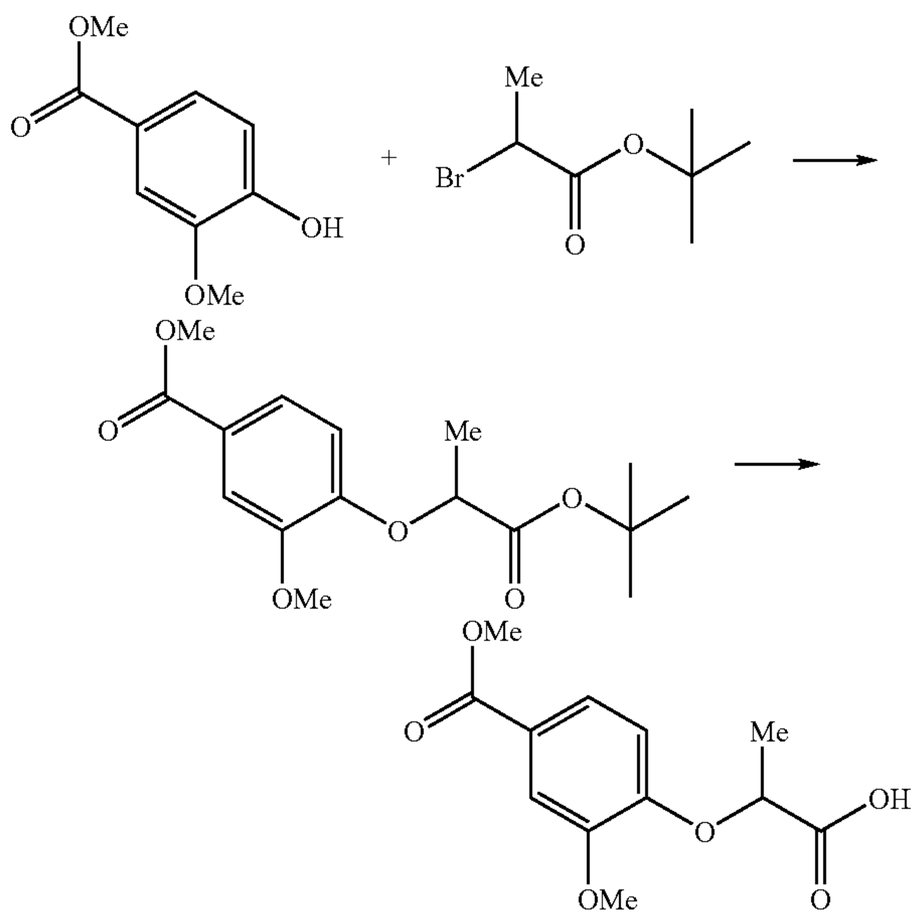
Preparation of Agent A:

(1) Preparation of 2-(quinolin-5-yloxy)propanoic acid (A01):

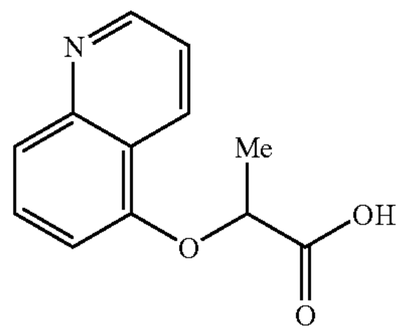
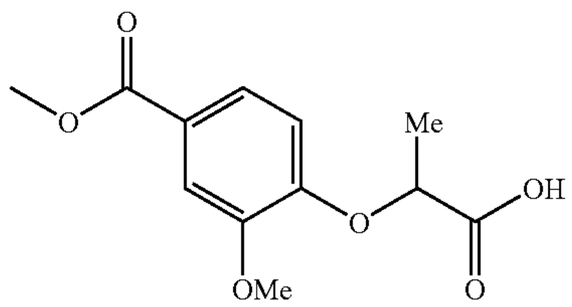


Quinolin-5-ol (0.868 g, 5.98 mmol) and tert-butyl 2-bromopropanoate (1.25 g, 0.97 mL, 5.98 mmol) and cesium carbonate (1.95 g, 5.98 mmol) were added into DMF (10 mL) in a 20 mL microwave vial equipped with a stir bar and sealed. The mixture was heated in Biotage microwave synthesizer for 1 hour at 100° C. The solvent was removed and the remained sticky oil was dissolved in DCM (7 mL) and TFA (7 mL). The mixture was stirred overnight. The reaction mixture was neutralized with sodium bicarbonate and organic layer was separated from the mixture. The aqueous layer was washed with DCM (2×10 mL), combined organics and acidified with 2N HCl. Aqueous was extracted with ethyl acetate, dried with sodium sulfate and concentrated to a dark orange oil. The crude product was dissolved in DCM (4 mL) and a pure product (0.855 g) precipitate out from the solution by adding diethyl ether (4 mL).

(2) Preparation of 2-(2-methoxy-4-(methoxycarbonyl)phenoxy)propanoic acid (A02):

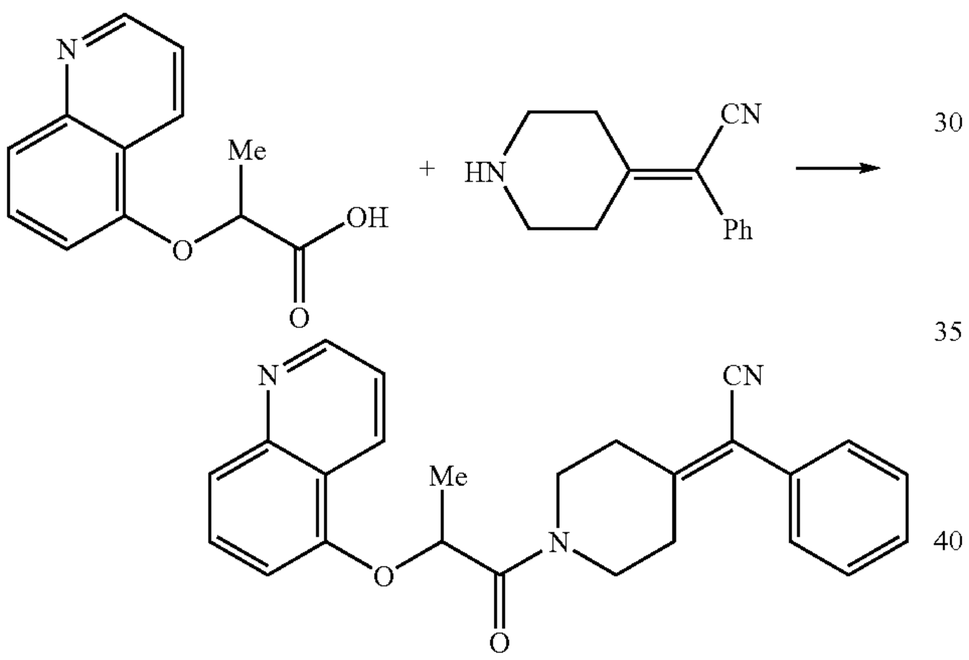


Methyl 4-hydroxy-3-methoxybenzoate (1.09 g, 5.98 mmol) and tert-butyl 2-bromopropanoate (1.25 g, 0.97 mL, 5.98 mmol) and cesium carbonate (1.95 g, 5.98 mmol) were added into DMF (10 mL) in a 20 mL microwave vial equipped with a stir bar and sealed. The mixture was heated in Biotage microwave synthesizer for 1 hour at 100° C. The solvent was removed and the remained sticky oil was dissolved in DCM (7 mL) and TFA (7 mL). The mixture was stirred overnight. The reaction mixture was neutralized with sodium bicarbonate and organic layer was separated from the mixture. The aqueous layer was washed with DCM (2×10 mL), combined organics and acidified to around pH5 with 2N HCl. Aqueous was extracted with DCM and then with ethyl acetate, dried with sodium sulfate and concentrated to an oil. The crude product was dissolved in DCM (4 mL) and a pure product (0.530 g) precipitate out from the solution by adding diethyl ether (4 mL).

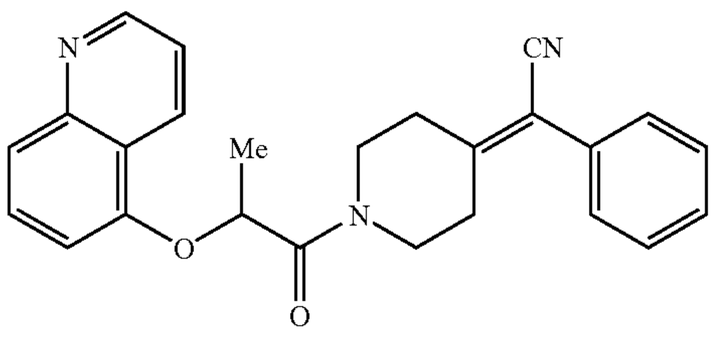
	Structure	MS (M + H)$^+$ Calcd.	MS (M + H)$^+$ Observ./ Retention Time/NMR
A-01		218.08	218.24 Rf = 1.15 min (column B) ^{1}H NMR (500 MHz, DMSO-d$_6$) δ9.06 (m, 1 H), 8.85 (d, 1 H), 7.68-7.81 (m, 3 H), 7.06 (d, 1 H), 5.16 (q, 1 H), 1.67 (d, 3 H).
A-02		255.09	255.24 Observed. Rf = 2.36 min (column A) ^{1}H NMR (500 MHz, DMSO-d$_6$) δ13.13 (b, 1 H), 7.53 (m, 1 H), 7.47 (m, 1 H), 4.91 (m, 1 H), 3.81 (d, 3 H), 1.52 (d, 3 H).

Preparation of Compound of Formula I

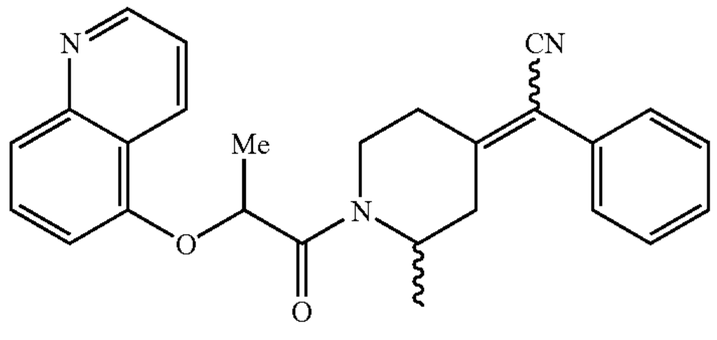
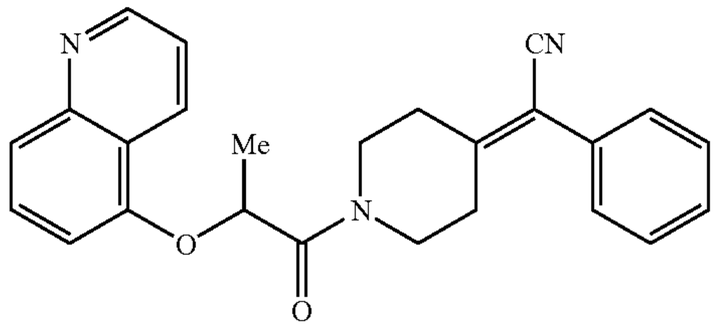
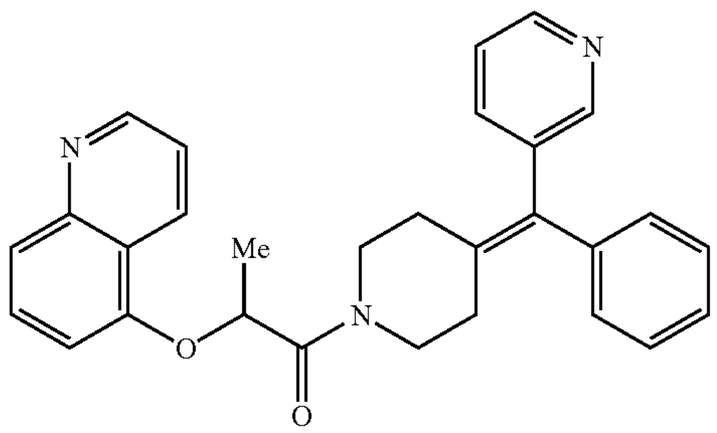
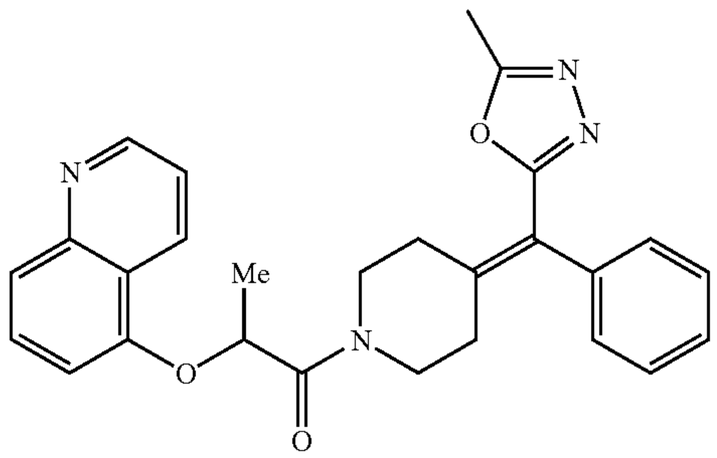
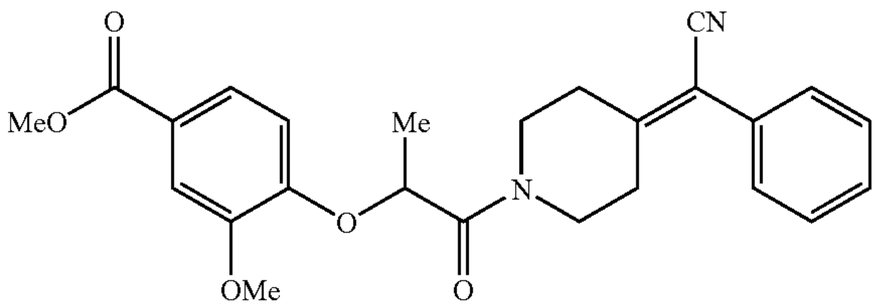
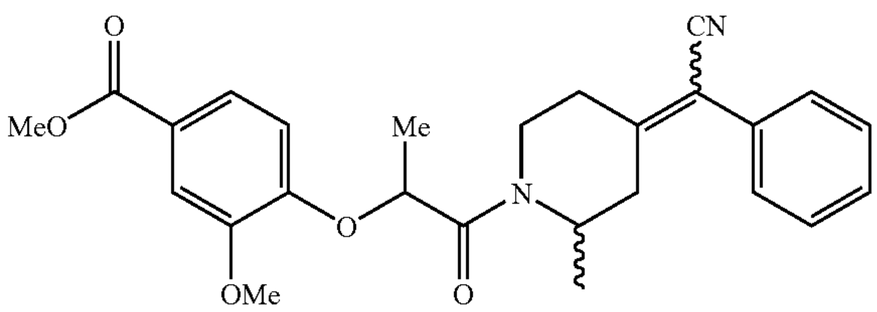
A general procedure, exemplified by the following reaction:



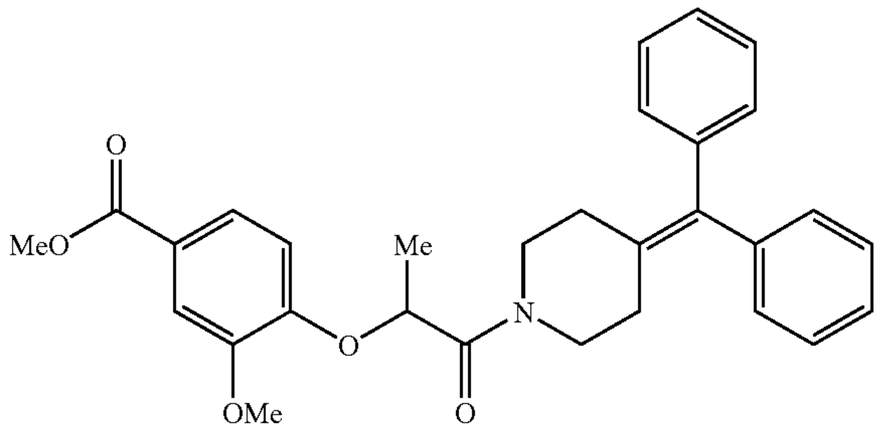
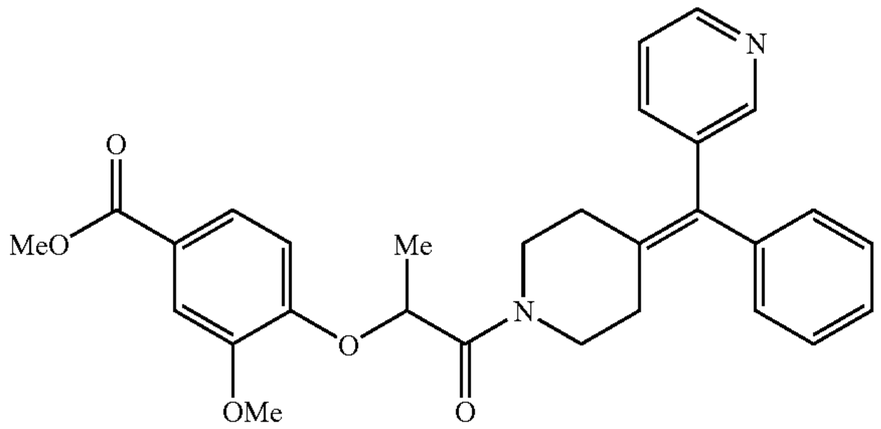
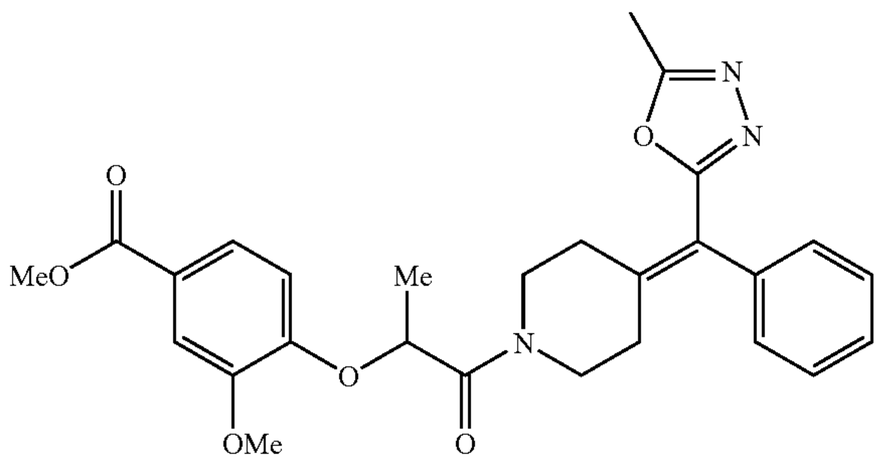
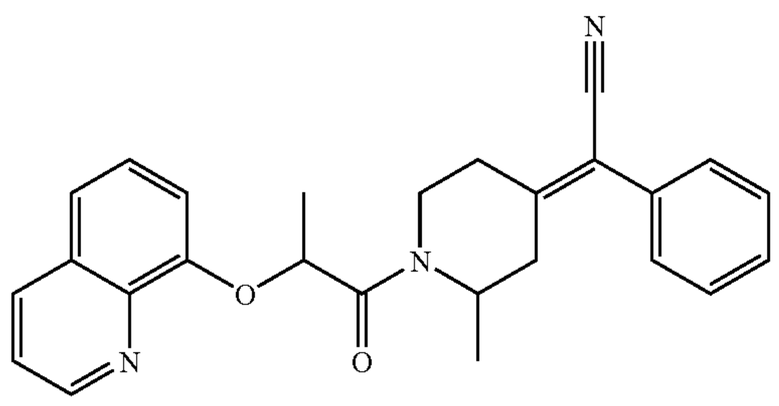
2-(quinolin-5-yloxy)propanoic acid, A01 (23.3 mg, 92 umol), TBTU (32.8 mg, 102 umol) and DIPEA (35.7 mg, 276 umol) in DMF (1 mL) were added into a 1-dram vial, followed by addition of 2-phenyl-2-(piperidin-4-ylidene)acetonitrile in DMF (0.5 mL). The vial was capped and shaken at room temperature overnight. The reaction was monitored by the following analytical LC-MS method and the product was purified by prep-HPLC using the following HPLC purification method.

Structure	MS (M + H)$^+$ Calcd.	MS (M + H)$^+$ Observ./HPLC Retention Time/NMR
	398.19	398.21 Rf = 1.34 min (column A) ^{1}H NMR (500 MHz, CDCl$_3$) δ9.28-9.32 (m, 1 H), 9.01 (s, 1 H), 8.46 (m, 1 H), 7.91 (m, 2 H), 7.30-7.38 (m, 5 H), 7.07 (m, 1 H), 5.36 (m, 1 H), 3.82 (m, 2 H), 3.62 (m, 2 H), 2.70-2.83 (m, 2 H), 2.41-2.50 (m, 2 H), 1.82 (m, 3 H)

-continued

Structure	MS (M + H)+ Calcd.	MS (M + H)+ Observ./HPLC Retention Time/NMR
	412.20	412.21 Rf = 1.28 min (column A)
	449.20	449.23 Rf = 1.6 min (column A)
	450.22	450.21 Rf = 1.24 min (column A)
	455.21	455.21 Rf = 1.26 min (column A)
	435.19	435.22 Rf = 1.41 min (column A)
	449.21	449.22 Rf = 1.36 min (column A)

-continued

Structure	MS (M + H)$^+$ Calcd.	MS (M + H)$^+$ Observ./HPLC Retention Time/NMR
	486.23	486.23 Rf = 1.66 min (column A)
	487.22	487.22 Rf = 1.29 min (column A)
	492.21	492.26 Rf = 1.23 min (column A)
	412.19	412.23 Rf = 1.26 min (column A)

Biology

"μM" means micromolar;

"mL" means milliliter;

"μl" means microliter;

"mg" means milligram;

The materials and experimental procedures used to obtain the results reported in Tables 1-2 are described below.

Cells:

Virus production—Human embryonic Kidney cell line, 293T, was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, Calif.) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis, Mo.).

Virus infection-Human epithelial cell line, HeLa, expressing the HIV-1 receptor CD4 was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, Calif.) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis, Mo.) and supplemented with 0.2 mg/mL Geneticin (Invitrogen, Carlsbad, Calif.).

Virus-Single-round infectious reporter virus was produced by co-transfecting human embryonic Kidney 293 cells with an HIV-1 envelope DNA expression vector and a proviral cDNA containing an envelope deletion mutation and the luciferase reporter gene inserted in place of HIV-1 nef sequences (Chen et al, Ref. 41). Transfections were performed using lipofectAMINE PLUS reagent as described by the manufacturer (Invitrogen, Carlsbad, Calif.).

Experiment:

HeLa CD4 cells were plated in 96 well plates at a cell density of 1×10^4 cells per well in 100 μl Dulbecco's Modified Eagle Medium containing 10% fetal Bovine serum and incubated overnight.

Compound was added in a 2 μl dimethylsulfoxide solution, so that the final assay concentration would be ≦10 μM.

100 μl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was then added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 200 μl per well.

Virally-infected cells were incubated at 37 degrees Celsius, in a CO_2 incubator, and harvested 72 h after infection.

Viral infection was monitored by measuring luciferase expression from viral DNA in the infected cells using a luciferase reporter gene assay kit, as described by the manufacturer (Roche Molecular Biochemicals, Indianapolis, Ind.). Infected cell supernatants were removed and 50 μl of lysis buffer was added per well. After 15 minutes, 50 μl of freshly-reconstituted luciferase assay reagent was added per well. Luciferase activity was then quantified by measuring luminescence using a Wallac microbeta scintillation counter.

The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

An EC_{50} provides a method for comparing the antiviral potency of the compounds of this disclosure. The effective concentration for fifty percent inhibition (EC_{50}) was calculated with the Microsoft Excel Xlfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four paramenter logistic model (model 205). The EC_{50} data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

Results:

TABLE 1

Biological Data Key for EC_{50}s

Compounds with EC_{50}s >1 μM	Compounds with EC_{50} <=1 μM
Group B	Group A

TABLE 2

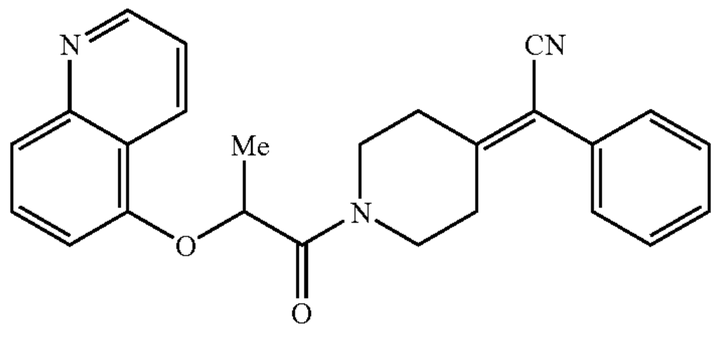
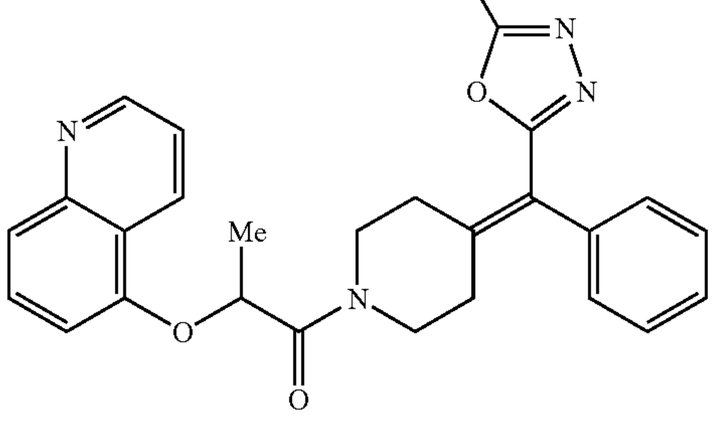
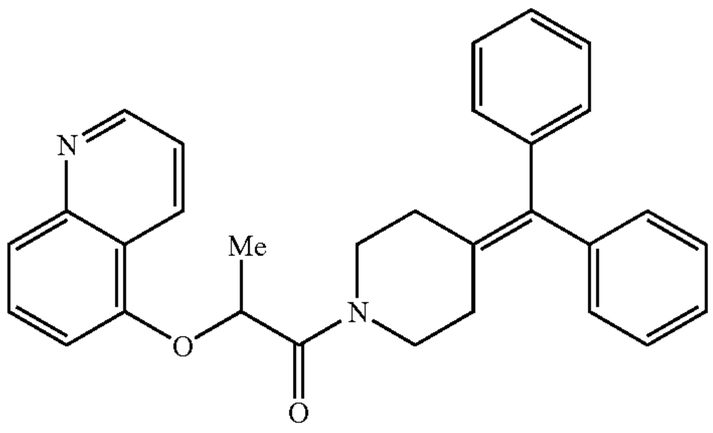
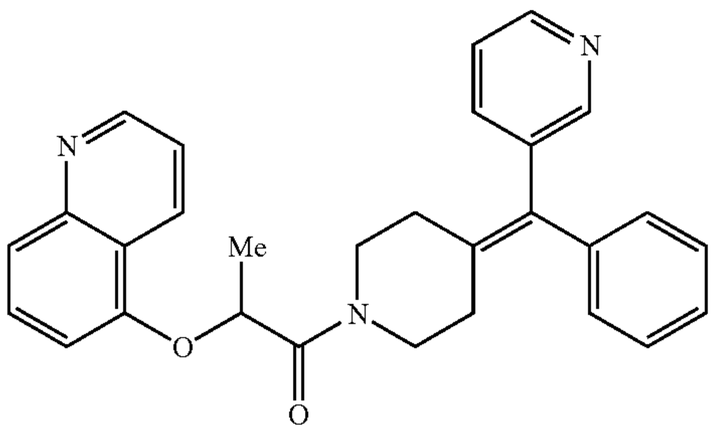
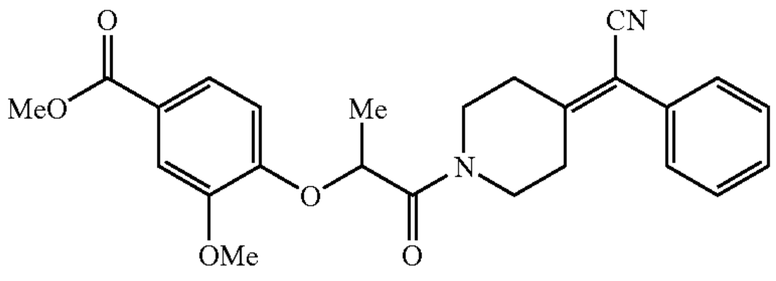
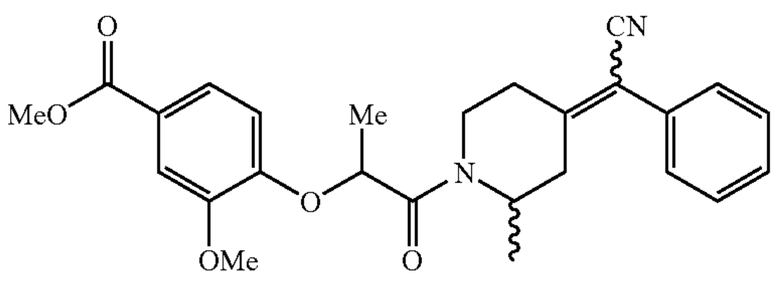
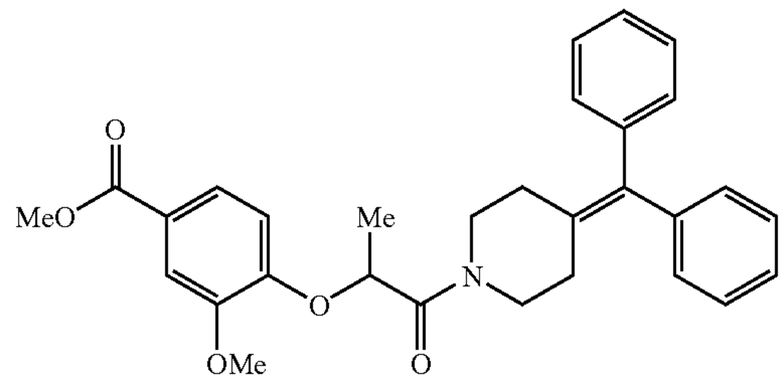
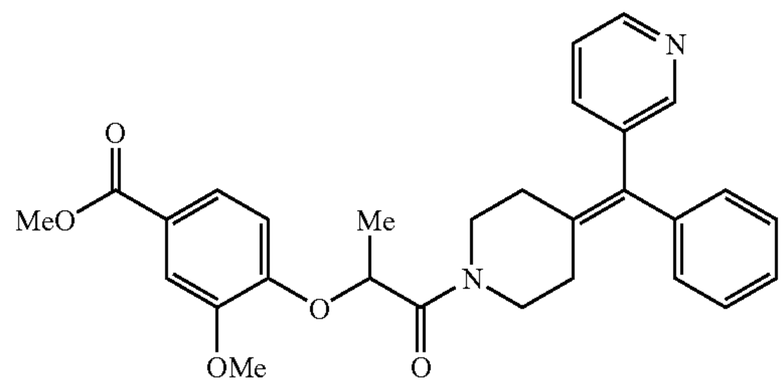
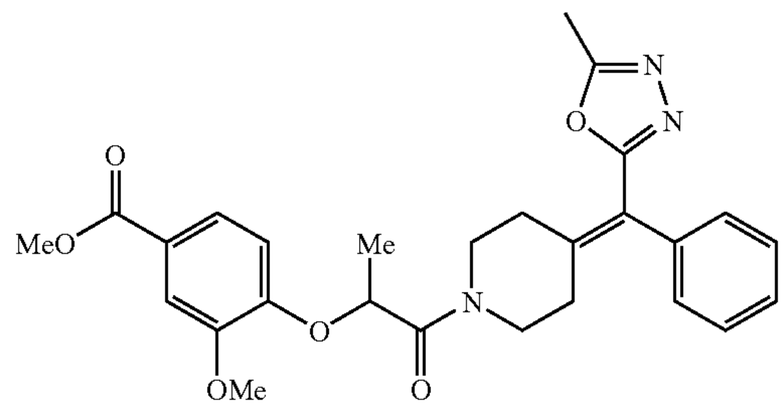
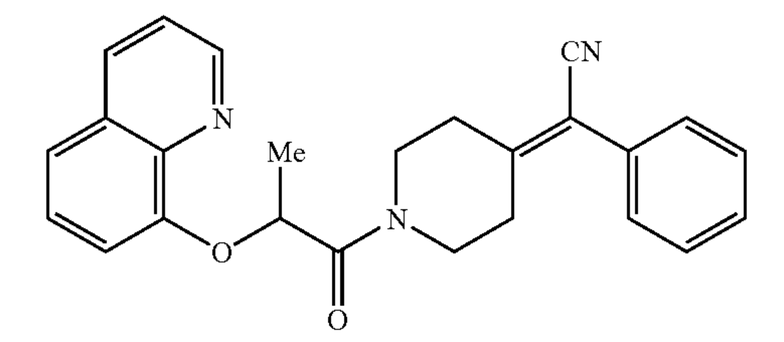
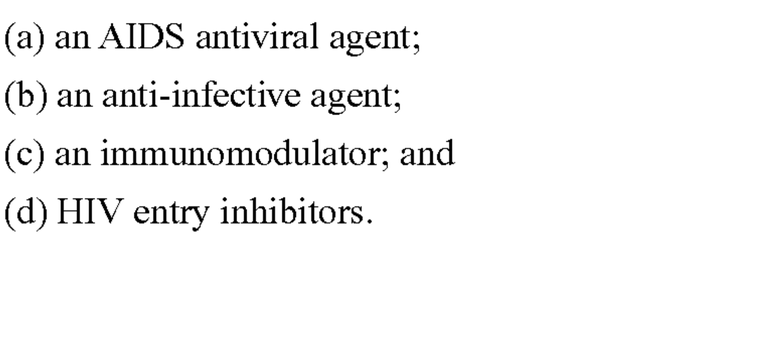
Structure	EC_{50} Group from Table 1
	A
	A
	B
	B
	B
	A
	A

TABLE 2-continued

Structure	EC_{50} Group from Table 1
	A
	B
	A
	A

What is claimed is:

1. A compound defined by the following formula, or pharmaceutically acceptable salts thereof:



2. A pharmaceutical composition which comprises an antiviral effective amount of the compound, or pharmaceutically acceptable salts thereof, as claimed in claim **1**, and one or more pharmaceutically acceptable carriers, excipients or diluents.

3. The composition of claim **2** further comprising a second compound having anti-HIV activity.

4. The pharmaceutical composition of claim **2**, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

(a) an AIDS antiviral agent;

(b) an anti-infective agent;

(c) an immunomodulator; and

(d) HIV entry inhibitors.

* * * * *